UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,731	12/15/2003	Eberhard Weihe	029310.52995US	6798

23911 7590 06/14/2005

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
STANDLEY, STEVEN H	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,731	WEIHE ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,7-12,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *5,6,13 and 16-32* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/05&~~5/06~~*. 5/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. It is noted that in the paper dated 4/13/05 the applicant has elected Group I, containing claims 1-15, without traverse, and SEQ ID NO: 4 *with traverse.* Applicant argues that the further restriction requirement meets the requirements set forth in *In Re Harnish* for a proper Markush group. Applicant states that all of the polypeptide sequences are very similar, and share a common utility. The examiner has considered this argument and it is found to be non-persuasive. Each individual SEQ ID NO: represents a patentably distinct polypeptide that is not obvious over the other, and would require separate searches by the examiner, which would represent a serious search burden on the examiner. No common structure has been disclosed as being linked to a common function. Therefore there is no unity within the Markush group. However, if applicant will stipulate on the record that each sequence is obvious over the other, the examiner would consider withdrawing the further restriction requirement to SEQ ID NO: 4. The election of SEQ ID NO: 4 is maintained and therefore claims 1-4, 7-12, and 14-15 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 7-12, and 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying substances that bind the polypeptide of SEQ ID NO: 4, does not reasonably provide enablement for a method for detecting a pain-regulating substance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention is comprised of incubating a test substance with a biomolecule, or a biomolecule synthesized in a cell, which is a sodium-dependent glutamate transporter, and then measuring the binding or "at least one functional parameter modified by the binding of the test substance." However, the method is directed to "A method for detecting a pain-regulating substance," *which cannot be measured* by the instant method. Pain is a sensation that "can be modulated by a wide range of behavioral experiences—the joy of childbirth can suppress pain, whereas fear of the dentist can intensify otherwise innocuous pain [first paragraph, Pain and Analgesia, Chapter 27,

Principles of Neural Science. Kandel and Schwartz, eds.] " It is further stated that "A distinction needs to be made between pain and nociception. Nociception refers to the reception of signals in the central nervous system evoked by activation of specialized sensory receptors (nociceptors) that provide information about tissue damage. Not all noxious stimuli that activate nociceptors are necessarily experienced as pain. Pain is a *perception* of an aversive or unpleasant sensation..."

Given that pain is a *perception*, which clearly requires an entire organism, and that mere activation of the neural pathways and proteins related to nociception is insufficient to be perceived as pain, the instant method cannot be a method for detecting a pain-regulating substance because it cannot measure pain.

The state of the prior art suggests the standard for detecting substances that modulate pain are animal models of pain. For instance, Leem et al. (2001) measure the amount of pressure applied to a rats paw before the rat withdraws its paw in pain (see abstract). They also measure the 'paw pressure threshold' in the presence of a compound, an NMDA receptor (which is a glutamate receptor) antagonist, and determined that the presence of the compound increased the 'paw pressure threshold,' which is reasonably a behavioral measure of pain experienced by the animal.

The predictability of the art is low with respect to the effect of molecules that are known to bind to and modulate a protein (which the instant method recites), and their affect on pain in animal models. For instance, in the animal model of pain used by Leem et al above, an NMDA receptor antagonist which binds and inhibits the NMDA receptor is effective at modulating pain (see abstract, and figure 2, page 157 of Leem et

al). However, in another model, the 'spared nerve injury' model of neuropathic pain, an NMDA receptor antagonist is ineffective at modulating pain (Erichsen et al., 2002; see line 10 of the abstract). Thus, both of these models measure pain, and yet a molecule known to bind and antagonize the NMDA receptor has the opposite results in the two different models.

There are no working examples in the specification of how applicant intends to measure pain in an in vitro method or in vivo method, nor what 'functional parameters' might be directly related to pain. The specification discloses in Example 5 an assay of a 'functional parameter' which is an in vitro assay to assess whether purified BNPI will ***phosphorylate*** a substrate to a lesser degree in the presence of a test compound which would indicate the test compound is an inhibitor. Applicant is respectfully reminded that the instant polypeptides are ***Glutamate Transporters*** with no known kinase activity, and none disclosed in the specification. Moreover, there is clearly no nexus made between the degree of phosphorylation and the perception of pain, which is what the method is recited as detecting. There is no guidance in the specification as to how the substances tested in the instant method could be determined to be pain-regulating in the instant assay.

Therefore, given the nature of the invention, the state of the prior art, the predictability of the art, the lack of working examples or specific guidance in the specification, the amount of experimentation necessary for one skilled in the art to make and use the instant method is undue.

3. Claims 1-4, 7-12, and 14-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to testing "at least one functional parameter modified by the binding of the test substance to the protein or part of protein." The specification defines a 'functional parameter' as 'measurement parameters of an experiment which correlate with the function of a protein.' There is no structural limitation on the protein(s) function(s) to be measured in the presence of the test compound. Thus, the claim is drawn to measuring some (unknown and undescribed) function of an unknown genus of proteins (or tissues, or organisms) that may relate to the function of the instant polypeptide of SEQ ID NO: 4 when the test compound is bound to it. Claim 11 further recites measurement of the regulation, inhibition, or activation of (unknown and undescribed) receptors, ion channels or enzymes. Claim 12 further recites measuring at least one functional parameter modified by the test substance via measurement of the modification of gene expression, the ionic medium, the pH, the membrane potential the enzyme activity or the concentration of 2^{nd} messenger, but the specification fails to disclose sufficient measurements for the claimed protein or any other protein.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only measurement of the function of the isolated polypeptide of SEQ ID NO: 4 meets the written description requirement, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-4, 7-12, and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "a method of detecting a pain-regulating substance" in claim 1 is used by the claim 1 to mean "The term pain-regulating here relates to ***a potential*** regulating influence on the physiological pain event, in particular to an analgesic action [page 6 of specification, emphasis added]", while the accepted meaning is "a method of

detecting a pain-regulating substance" The term is indefinite because the specification does not clearly redefine the term.

5. Claim 1 is further indefinite because the term "stringent conditions" is not defined by the specification and is therefore indefinite because it is not known what the meets and bounds of "stringent" are, or exactly what defines 'stringent conditions.'

6. Claim 1 is further indefinite because step (a) recites incubating a test compound with a biomolecule...or part protein...or a cell...or cell preparation. However, step (b) measures the binding of the test substance to the protein or part of the protein *synthesized by the cell* or measuring at least one functional parameter..." It is unclear whether step (b) is practiced with the biomolecule of the first part of (a), or whether step (b) is meant to be practiced only with a cell synthesizing the biomolecule.

7. Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the final step wherein the conditions for determining if the compound has detected a pain regulating substance are set forth. Claims 2-4, 7-12, and 14-15 are rejected as depending upon the indefinite claim 1.

8. Claim 1, 3, and 11 are indefinite for using the term 'functional parameter' in the instant method is indefinite. The specification defines a 'functional parameter' as 'measurement parameters of an experiment which correlate with the function of a protein.' This definition is circular and indefinite. Parameters are limits or boundaries which can be varied, such as temperature, in an experiment (see appendix A, the

definition of parameter), however applicant has used parameter to mean something else which cannot be understood and is therefore indefinite.

9. Claims 2-4, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term 'genetic engineering' in the claims is indefinite. The specification defines 'manipulation by genetic engineering' to mean "the manipulation of cells, tissues, or organs such that genetic material is introduced." 'Genetic material' could be an indefinite amount of genomic DNA, recombinant DNA, or RNA. It is also unclear by what means they are to be introduced, for instance, the definition is easily encompassed by infection with the common cold. Claims 8 is rejected for depending from an indefinite claim.

10. Claim 4 is indefinite because it recites expression of a G-protein. However, it is unclear as to how this G-protein which is not endogenously expressed is part of the invention. The claims are directed to glutamate transporters, which are sodium dependent in some cases, and in some cases chloride activated, and which may or may not require ATP. However, none of them are known as, nor are they disclosed as in the specification, G-protein coupled transporters. In fact, a G-protein coupled transporter is not known in the art. Therefore it is not evident how this limitation relates to the claimed method.

11. Claim 9 is indefinite because it recites a 'native mammalian cell.' This is indefinite because the definition of a 'cell' as given in the specification is "Cell: The cell

is a self-regulating, open system which is in a flow equilibrium with its environment by permanent exchange of matter and has its own metabolism and ability to multiply. The cell can be cultured separately or can be part of a tissue, in particular from an organ, and can exist there individually or also in a cell union." It is not clear how 'native' further limits the definition of a cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Edwards et al (US patent publication number 2002/0098473, claiming priority to July 25, 2000).

Edwards et al. disclose contacting test compounds to a polypeptide of 98.5% (see appendix B) identity to that of SEQ ID NO: 4, which is called Vglut1, to determine if the compound binds (sections 186 and 187 on page17). It is further disclosed in section 88, page 9, "that inhibition of glutamate can also be useful in anesthesia and the management of pain (e.g. neuropathic pain)", which meets the limitations of both

steps (a) and (b) of claim 1, and 14. Edwards further disclose screening methods in which glutamate uptake into a cell is modulated in section 6 on page 1 and the use of recombinant expression in cells in section 209 of page 19, reasonably meeting the limitation of a genetically manipulated cell (claim 2) and a genetically manipulated cell which allows the measurement of at least one function modified by the binding of a test compound (claim 3). Claims 36 and 37 on page 35 of Edwards et al. recite the culturing of the polypeptides in a cell such that they are expressed, meeting the limitations of claim 7. Figure 13A and the description of the figure in section 73 on page 8 disclose the making of a stable cell line, which meets the limitations of claim 8. Section 209, page 19 of Edwards et al. discloses recombinant expression of the polypeptide in yeast, which meets the limitations of claim 9. Competition assays are disclosed in section 126 on page 12 of Edwards et al., meeting the limitations of claim 10. Gene expression of Vglut1 is disclosed as being inhibited by administration of a test compound in section 15, page 2 of Edwards, et al., meeting the limitations of claim 12.

Conclusion

No claims are allowed.

Any inquiry concerning this communication should be directed toward examiner Steven Standley (Ph: 571-272-3432). The examiner can normally be reached Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the Steven Standley fail, the examiners' supervisor, Anthony Caputa, can be reached at (571 272-0829).

Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (toll free) 866-217-9197.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Steven H. Standley, Ph.D.